Remarks

I. Status of the Claims

Claims 141-158 stand rejected by the Office Action dated 16 April 2003. In response, please cancel all pending claims (Claims 141-158) and add new Claims 159 and 160.

II. The Specification Provides a Written Description of the Invention of Claims 159-160 in Compliance with 35 U.S.C. § 112

The Applicants assert that no new matter is added by the addition of Claims 159 and 160. Bases for these claims are found throughout the specification, particularly in the following locations in the published PCT application (WO 00/04913):

Table 1. Bases for Claim 159.

	Basis in specification	Actual wording in specification
pharmaceutically acceptable	Page 31, lines 6-13	"the invention provides for stable formulations . . . comprising FSH or FSH variant in a **pharmaceutically acceptable** formulation"
solution formulation	Page 31, lines 6-11	"the invention provides for . . . **solution**s and **formulation**s"
comprising human FSH and a preservative in an aqueous diluent	Page 6, lines 14-20	"**comprising FSH . . . and a preservative. . . in an aqueous diluent**"
	Page 10, lines 7-9	"FSH as used herein refers to the FSH produced as a full length mature protein which includes . . . **human** FSH or 'hFSH'"

	Basis in specification	Actual wording in specification
the preservative is selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, benzalkonium chloride, benzethonium chloride, sodium dehydroacetate, thimerosal, and mixtures thereof,	Page 7, lines 9-14	"**preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben** (methyl, ethyl, propyl, butyl and the like), **benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal**, derivatives thereof, or **mixtures thereof**
concentration of FSH is 5.0 μg/mL to 2 mg/mL	Page 35, lines 8-9	"hormone **concentrations** are preferably about **5.0 μg/ml to 2 mg/ml**"
FSH consists of an α-subunit having SEQ ID NO:5 and a ß-subunit having SEQ ID NO:6, held together by noncovalent interactions	Page 3, lines 4-14	"The members of this family are heterodimers, **held together** generally **by noncovalent interactions** between the two different subunits. The human **FSH** (hFSH) heterodimer **consists of** (i) a mature 92 amino acid **alpha subunit** . . .; **and** (ii) a mature 111 amino acid **beta subunit** that is unique to FSH . . . . The alpha and beta subunits bind non-covalently."
	Page 10, lines 16-19	The protein sequence of the **human FSH alpha subunit** is provided in **SEQ ID NO: 5**, and the protein sequence of the **human FSH beta subunit** is given in **SEQ ID NO:6**.
formulation is suitable for multi-dose administration by injection	Page 9, lines 1-2	"are **suitable for** extended or **multiple use**"
	Page 9, lines 10-13	"suitable for use in **injectable** . . . systems, e.g., but not limited to, . . . subcutaneous, . . . intramuscular or parenteral . . . liquid formulation"

	Basis in specification	Actual wording in specification
	Page 7, lines 6-7	"invention provides a process for preparing at least one **multi-dose** formulation"

Bases for Claim 160 are the same as for Claim 159, with the following exceptions:

	Basis in specification	Actual wording in specification
comprising an FSH variant and a preservative in an aqueous diluent	Page 6, lines 14-20	"**comprising . . . a FSH variant and a preservative. . . in an aqueous diluent**"
FSH consists of an α-subunit having SEQ ID NO:5 and a ß-subunit having SEQ ID NO:6, held together by noncovalent interactions	Page 12, lines 12-16	"**FSH variants** referred to herein are the carboxy terminal deletions of the **beta subunit** . . . provided in **SEQ IDS NOS:11**, 12, and 13"
	Page 13, line 35 through page 14, line 5	(f): **α-subunit:(SEQ ID NO:5)** APDVQDCPECTLQENPFFSQPGAPILQC MGCCFSRAYPTPLRSKKTMLVQKNVTSE STCCVAKSYNRVTVMGGFKVENHTACHC STCYYHKS **ß-subunit:(SEQ ID NO:11)** NSCELTNITIAIEKEECRFCISINTTWC AGYCYTRDLVYKDPARPKIQKTCTFKEL VYETVRVPGCAHHADSLYTYPVATQCHC GKCDSDSTDCTVRGLGPSYCSFGE

III. Claims 159 and 160 Are Not Obvious Under 35 U.S.C. § 103(a)

A. The Rejections

The Examiner rejected Claims 141, 142, 145, 147, 152, 154, 156, and 158 (all of which are now canceled) under 35 U.S.C. § 103(a) as unpatentable over Andya, *et al.* (U.S. Patent No. 6,267,958, "Andya"). The Applicants assert that the new Claims 159 and 160 are patentable over Andya.

The Examiner alleged that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Andya to make the instant invention of stable, pharmaceutical [sic] acceptable, solution formulation suitable form multi-use comprising FSH, benzyl alcohol or m-cresol." The Examiner further alleged, "The motivation and expected success is provided by Andya who teaches stable pharmaceutical multi-use formulations and discloses FSH as a suitable protein for use in the formulation. Andya also teaches that a preservative, such as benzyl alcohol or m-cresol, can be added to the diluent to reduce

bacterial action in the reconstituted formulation, thus facilitating the production of a multi-use reconstituted formulation."

The Examiner further rejected Claims 143, 146, 149-155, and 157 (all of which are now canceled) under 35 U.S.C. § 103(a) under 35 U.S.C. § 103(a) as unpatentable over Andya in view of Skrabanja *et al.* (EP 0 853 945 A1; "Skrabanja"). The Applicants assert that the new Claims 159 and 160 are patentable over Andya in view of Skrabanja.

The Examiner alleged, "The motivation and expected success is provided by Skrabanja and Andya. Skrabanja teaches the concentrations of FSH and that various forms of FSH in [sic] can be used in stable multi-use liquid pharmaceutical formulations. Andya teaches stable pharmaceutical multi-use formulations and discloses FSH as a suitable protein and benzyl alcohol as a preservative to reduce bacterial action in multi-use reconstituted formulations."

Lastly, the Examiner rejected Claims 144 and 148 (now canceled) under 35 U.S.C. § 103(a) as unpatentable over Andya and Skrabanja in view of Boime, *et al.* (U.S. Patent No. 6,238,890; "Boime"). The Applicants assert that the new Claims 159 and 160 are patentable over Andya in view of Skrabanja and Boime.

The Examiner stated that Boime teaches SEQ ID NO:5 and SEQ ID NO:11. She alleged, "The motivation and expected success is provided by Andya who teaches the use of benzyl alcohol and m-cresol in stable multi-use formulations comprising FSH. Skrabanja teaches that different forms of FSH can be used in the formulations including analogs, recombinant, modified glycosylated and other forms. Boime teaches that single chain forms are unique starting materials for identifying truncated forms with the activity of the dimers and using variants of the ß subunit of FSH will also help identify agonists and antagonist of the glycoprotein hormone activity."

As Claims 141-158 have been canceled, all outstanding rejections under § 103(a) are obviated. The evidence and comments below demonstrate that the new claims, Claim 159 and 160, are patentable over the cited art.

B. Claims 159 and 160 Are Not *Prima Facie* Obvious

To establish a prima facie case of obviousness, the Examiner must show: (1) motivation or suggestion to modify or combine the references; (2) reasonable

expectation of success; and (3) the combined references must teach all claim limitations. M.P.E.P. § 2143.

The Applicants assert that Claims 159 and 160 are patentable over Andya. The Examiner cited Andya (U.S. Patent No. 6,267,958), alleging that that it teaches a stable FSH formulation and that a preservative can be added to that formulation. However, **Andya's formulation is well outside the FSH concentration range of Claim 128**. This is a significant difference: Andya teaches away from the concentrations of Claims 159 and 160. Purposefully, Andya provides reconstituted protein formulations of very high concentration—"generally 50 mg/mL or more"—as "such high protein concentrations are particularly useful where the formulation is intended for subcutaneous administration." Andya, col. 2, lines 6-9. Andya lacks the motivation/suggestion of modification or combination that is required for the prima facie case of obviousness. Additionally, Andya lacks a reasonable expectation of success. A person of skill in the art would recognize that the protein formulation of Andya—at 25 to 10,000 times more concentrated than the FSH concentration of Claims 159 and 160—would not lead to a reasonable expectation of success at lower concentrations.

Finally, Andya does not teach all claim limitations of the instant application. Andya provides no guidance regarding selection of preservatives that are compatible with an FSH formulation. Andya provides "examples of potential preservatives" which include octadecyldimethylbenzyl ammonium chloride, hexamethonium chloride, benzalkonium chloride (a mixture of alkylbenzyldimethylammonium chlorides in which the alkyl groups are long-chain compounds), benzethonium chloride, aromatic alcohols such as phenol, butyl and benzyl alcohol, allyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, 3-pentanol, and m-cresol. Although Andya's list overlaps in some respects with the Markush group in the instant application, **Andya provides no suggestion or motivation regarding two preservatives of Claims 159 and 160: sodium dehydroacetate and thimerosal. Nor does Andya suggest the FSH variant of Claim 160**. Thus, Andya does not teach all limitations of Claims 159 and 160. Because many of Andya's named preservatives are not included in Claims 159 and 160, Andya cannot properly form the basis of an obviousness rejection without impermissibly picking and choosing

from within Andya's entire disclosure. In light of these considerations, Claims 159 and 160 are not prima facie obvious and, thus, are patentable over Andya.

The Applicants further assert that Claims 159 and 160 are patentable over the combination of Andya with Skrabanja (EP 0 853 945). Andya and Skrabanja do not suggest the desirability of combination with each other. **Andya specifically teaches that protein concentrations of 50 mg/mL are desirable, teaching away from lower concentrations. This provides no motivation to combine Andya with Skrabanja—a patent specifically directed to FSH concentrations between 2 µg/mL and 200 µg/mL!** This is a significant difference; Andya would require FSH that is 250 to 25,000 times more concentrated than Skrabanja teaches.

Additionally, **Skrabanja does not express or imply any desire to provide a preserved formulation, which Andya allegedly provides**. Skrabanja discloses a sterile aqueous solution of FSH which may be provided in a cartridge containing one or more therapeutic doses. However, neither sterility nor "one or more" doses necessarily suggest the use of a preservative. Sterility refers to the condition of the solution when the cartridge is sealed; it does not indicate the use of an antimicrobial preservative. Skrabanja provides no information on how long the sterile solution can be safely used. More importantly, **Skrabanja does not even hint that a preservative could be used in its solution formulations**. The skilled artisan would have no motivation to combine Andya with Skrabanja.

Moreover, the addition of Skrabanja to Andya does not resolve Andya's failure to teach all claim limitations. Because Skrabanja does not mention preservatives, even a **combination of Skrabanja with Andya does not teach two preservatives in the claims—sodium dehydroacetate and thimerosal**. This failure to teach all claim limitations as well as the lack of motivation in the previous paragraph indicate that no prima facie case of obviousness has been established by the combination Skrabanja with Andya. Claims 159 and 160 are patentable over the combination of Skrabanja with Andya.

The Applicants further assert that Claims 159 and 160 are patentable over Andya in view of Skrabanja and Boime (U.S. Patent No. 6,238,890). Boime is cited by the Examiner because it discloses the variant comprising the α-subunit having SEQ ID NO:5 and the ß-subunit having SEQ ID NO:11. However, Boime is not applicable to Claim 159 because Claim 159 only claims human FSH, FSH comprising the α-

subunit having SEQ ID NO:5 and the ß-subunit having SEQ ID NO:6. Boime does not disclose human FSH. Thus, combining Boime with Skrabanja and Andya does nothing resolve the deficiencies in the prima facie case of Skrabanja with Andya. Hence, a prima facie case of obviousness against Claim 159 cannot be met, and Claim 159 is patentable over the combination of Boime with Skrabanja and Andya.

Additionally, Boime is directed to FSH variants that are covalently bonded to form a single-chain. Covalently bonded FSH subunits are outside the scope of both Claims 159 and 160. Boime provides no suggestion or motivation to make a preserved non-covalently bonded human FSH formulation. In fact, **Boime specifically teaches away from non-covalent bonding by teaching that covalent bonding stabilizes the protein**. Thus, there is no motivation to combine Boime with Andya and Skrabanja, and no prima facie case of obviousness can be met. In light of this, Claims 159 and 160 are patentable over Boime in view of Andya and Skrabanja.

The Applicants assert that no *prima facie* case of obviousness has been established against Claims 159 and 160.

IV. The Rejections for Nonstatutory Double Patenting Should Be Removed

The Examiner has provisionally rejected Claims 141-158 over copending Application No. 09/973,918 (X-12383P) for nonstatutory double patenting. This provisional rejection is obviated because the copending application has been abandoned. Thus, the Applicants respectfully request that the Examiner remove this provisional rejection.

The Examiner has also provisionally rejected Claims 141-158 over copending Application No. 09/744,431 (X-12383M) nonstatutory double patenting. These claims have been canceled, thereby obviating the provisional rejections. Moreover, because Application No. 09/744,431 and the instant application are commonly owned, the Applicants offer to submit a terminal disclaimer of the instant application to overcome any rejections for double patenting that the Examiner might allege against the new claims, Claims 159 and 160.

V. Conclusion

The Applicants assert that all rejections have been obviated by the amendments and remarks herein. In light of this, the Applicants respectfully request that the Examiner

enter this amendment and advance the application to issue.

Respectfully submitted,

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16 October 2003